

In the Claims

In Claim 36, at line 1, delete "~~any one of Claims 33-35~~" and substitute therefor --either Claim 33 or Claim 34--.

In Claim 37, at line 1, delete "~~any one of Claims 33-35~~" and substitute therefor --either Claim 33 or Claim 34--.

In Claim 38, at line 1, delete "~~any one of Claims 33-35~~" and substitute therefor --Claim 34--.

In Claim 42, at line 1, delete "~~any one of Claims 39-41~~" and substitute therefor --Claim 40--.

In Claim 48, at line 2, delete "~~first~~."

In Claim 48, at line 3, delete the first instance of "~~the~~" and insert therefor --a--.

In Claim 57, at line 2, delete "~~first~~."

In Claim 57, at line 3, delete the first instance of "~~the~~" and insert therefor --a--.

In Claim 58, at line 1, delete "~~52~~" and insert therefor --53--.

Please cancel Claims ~~35~~, ~~41~~ and ~~51~~ without prejudice and add the following new

Claims 59-86:

sub 53  
13:59. (New) A method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of that enzyme whose production by a cell evokes a responsive change in a phenotypic characteristic of the cell, other than the level of the enzyme in said cell per se, which comprises:

C2  
(a) providing a first mammalian cell line which produces the enzyme and exhibits the phenotypic response to the enzyme, said first cell line obtained by introducing a gene encoding the enzyme into a host cell by means of a first genetic vector into which said gene has been inserted, said gene being under the control of a promoter functional in said host cell, whereby said gene is expressed;

(b) providing a second mammalian cell line which produces the enzyme at a lower level than said first cell line, or does not produce the enzyme at all, and which exhibits the phenotypic response to the enzyme to a lesser degree or not at all, said second cell line obtained by introducing into a similar host cell a second genetic vector essentially identical to said first genetic vector except that it does not bear said gene insert;

(c) incubating the chemical agent with said first and second cell lines; and

(d) comparing the phenotypic response of said first cell line to the chemical agent with the phenotypic response of said second cell line to the chemical agent.

<sup>14</sup>60. (New) The method of Claim <sup>13</sup>59 wherein the chemical agent is a suspected inhibitor of the biological activity of the enzyme.

<sup>15</sup>61. (New) The method of Claim <sup>13</sup>59 wherein the chemical agent is a suspected activator of the biological activity of the enzyme.

<sup>16</sup>62. (New) The method of Claim <sup>13</sup>59 wherein the phenotypic response of said first cell line upon incubation with the chemical agent is a graded cellular response.

<sup>17</sup>63. (New) A method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of that enzyme whose production by a cell evokes a responsive change in a phenotypic characteristic, other than the level of the enzyme in the cell per se, which comprises:

(a) providing a first mammalian cell line which produces the enzyme and exhibits the phenotypic response to the enzyme, said phenotypic response being a graded cellular response;

(b) providing a second mammalian cell line which produces the enzyme at a lower level than said first cell line, or does not produce the enzyme at all, and which exhibits the phenotypic response to the enzyme to a lesser degree or not at all;

(c) incubating the chemical agent with said first and second cell lines; and

(d) comparing the graded cellular response of said first cell line to the chemical agent with the phenotypic response of said second cell line to the chemical agent.

<sup>110</sup>  
~~64~~. (New) The method of Claim <sup>117</sup>~~63~~ wherein the chemical agent is a suspected inhibitor of the biological activity of the enzyme.

<sup>119</sup>  
~~65~~. (New) The method of Claim <sup>117</sup>~~63~~ wherein the chemical agent is a suspected activator of the biological activity of the enzyme.

66. (New) The method of any one of Claims 33, 34 and 59 to 65 wherein the chemical agent directly interacts intracellularly with the enzyme.

67. (New) A method of determining whether a chemical agent that directly interacts with a protein is an inhibitor or activator of that protein whose production by a cell evokes a responsive change in a phenotypic characteristic of the cell, other than the level of the protein in the cell per se, which comprises:

(a) providing a first mammalian cell line which produces the protein and exhibits the phenotypic response to the biological activity of the protein, said first cell line obtained by introducing a gene encoding the protein into a host cell by means of a first genetic vector into which said gene has been inserted, said gene being under the control of a promoter functional in said host cell, whereby said gene is expressed;

(b) providing a second mammalian cell line which produces the protein at a lower level than said first cell line, or does not produce the protein at all, and which exhibits the phenotypic response to the biological activity of the protein to a lesser degree or not at all, said second cell line obtained by introducing into a similar host cell a second genetic vector essentially identical to said first genetic vector except that it does not bear said gene insert;

(c) incubating the chemical agent with said first and second cell lines, wherein the chemical agent is suspected of being an inhibitor or activator of the biological activity of the protein; and

(d) comparing the phenotypic response of said first cell line to the chemical agent with the phenotypic response of said second cell line to the chemical agent.

68. (New) The method of Claim 67 wherein the phenotypic response of said first cell line upon incubation with the chemical agent is a graded cellular response.

69. (New) A method of determining whether a chemical agent that directly interacts with a protein is an inhibitor or activator of that protein whose production by a cell evokes a responsive change in a phenotypic characteristic, other than the level of the protein in the cell per se, which comprises:

(a) providing a first mammalian cell line which produces the protein and exhibits the phenotypic response to the protein, said phenotypic response being a graded cellular response;

(b) providing a second mammalian cell line which produces the protein at a lower level than said first cell line, or does not produce the protein at all, and which exhibits the phenotypic response to the protein to a lesser degree or not at all;

(c) incubating the chemical agent with said first and second cell lines, wherein the chemical agent is suspected of being an inhibitor or activator of the biological activity of the protein; and

(d) comparing the graded cellular response of said first cell line to the chemical agent with the phenotypic response of said second cell line to the chemical agent.

70. (New) The method of any one of Claims 39, 40 and 67 to 69 wherein the chemical agent directly interacts intracellularly with the protein.

20.  
71. (New) A method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of the enzyme which comprises:

(a) providing a mammalian test cell which overproduces the selected enzyme relative to a mammalian control cell which produces the enzyme at a lower level or essentially does

not produce the enzyme, and wherein production of the enzyme in said test cell evokes a responsive change in a phenotypic characteristic of said test cell, other than the level of the enzyme in said test cell per se, said responsive change being a graded cellular response, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected enzyme with the chemical agent; and

(c) examining said treated test cell to determine whether it exhibits a change in said graded cellular response to the chemical agent.

<sup>21</sup>  
~~72~~ (New) The method of Claim ~~71~~<sup>20</sup> wherein said test cell is obtained by introducing a gene encoding the enzyme into a host cell, said gene being under the control of a promoter functional in said host cell, whereby said gene is expressed.

<sup>22</sup>  
~~73~~ (New) The method of Claim ~~72~~<sup>21</sup> wherein said gene is introduced into said host cell by means of a first genetic vector into which said gene has been inserted, and said control cell is obtained by introducing into a similar host cell a second genetic vector essentially identical to said first genetic vector except that it does not bear said gene insert.

<sup>23</sup>  
~~74~~ (New) The method of Claim ~~73~~<sup>22</sup> wherein examination for the graded cellular response to the chemical agent includes comparing the response of said treated cell to the response of a comparable untreated cell. *test cell?*

<sup>24</sup>  
~~75~~ (New) The method of Claim ~~74~~<sup>23</sup> wherein examination includes comparing the graded cellular response of said treated test cell to that of a comparably treated test cell which does not overproduce the selected enzyme.

<sup>25</sup>  
~~76~~ (New) The method of Claim ~~75~~<sup>24</sup> wherein examination includes comparing the graded cellular response of said test cell to the chemical agent with the phenotypic response of a second test cell to a known inhibitor or activator of the enzyme.

<sup>20 25</sup>  
~~77~~ 77. (New) The method of any one of Claims ~~71~~<sup>71</sup> to ~~76~~<sup>76</sup> wherein the chemical agent is a suspected inhibitor of the biological activity of the enzyme.

<sup>20 25</sup>  
~~78~~ 78. (New) The method of any one of Claims ~~71~~<sup>71</sup> to ~~76~~<sup>76</sup> wherein the chemical agent is a suspected activator of the biological activity of the enzyme.

79. (New) The method of any one of Claims 43 to 50 and 71 to 76 wherein the chemical agent directly interacts intracellularly with the protein.

80. (New) A method of determining whether a chemical agent that directly interacts with a protein is an inhibitor or activator of that protein which comprises:

(a) providing a mammalian test cell which overproduces the selected protein relative to a mammalian control cell which produces the protein at a lower level or essentially does not produce the protein, and wherein production of the protein in said test cell evokes a responsive change in a phenotypic characteristic of said test cell, other than the level of the protein in said test cell per se, said responsive change being a graded cellular response, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected protein with the chemical agent, wherein the chemical agent is suspected of being an inhibitor or activator of the biological activity of the protein; and

(c) examining said treated test cell to determine whether it exhibits a change in said graded cellular response to said chemical agent.

81. (New) The method of Claim 80 wherein said test cell is obtained by introducing a gene encoding the protein into a host cell, said gene being under the control of a promoter functional in said host cell, whereby said gene is expressed.

82. (New) The method of Claim 81 wherein said gene is introduced into said host cell by means of a first genetic vector into which said gene has been inserted, and said control